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ON THE PRODUCT DISTRIBUTION IN THE IODINATION OF PHENOL

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Summary: The product distribution in the iodination of phenol with I_2 in water solution is buffer and pH dependent with the ortho product increasing at low pH and low buffer concentration. This effect is attributed to different rates of proton transfer from the 4-iodo-2,5-; and 2-iodo-3,5-cyclohexadienone intermediate.

The kinetics of the iodination of phenol in water solution has been extensively studied with the aim of determining the nature of the iodinating agent[1]. However, no efforts have been made to determine the position of attack of the electrophile to the aromatic nucleus. Many papers where kinetic studies are carried out assume that the major isomer formed is the para one, as was reported by Holleman and Rinkes in 1911[2] . In connection with other studies that are being carried out in our laboratory, we have become interested in knowing the exact product distribution under different set of conditions. Much to our surprise, under most of our reaction conditions, which are similar to those reported in the literature for kinetic studies, the ortho isomer predominates (Table). Besides, the relative amount of products is highly dependent on the pH and buffer concentration. Compare for instance runs 1-3 where an increase in buffer concentration at constant pH changes the o/p ratio from 6.1 to 1.53.

At the same total buffer concentration a change in pH from 7.5 to 6.1 changes the o/p ratio from 2.1 to 8.2 (runs 2 and 4). In some of the experiments, particularly those where the concentration of I_2 and PhOH is similar a significant amount of dihalogenated phenol was formed, thus it was necessary to know whether the dihalogenation reaction consumes the ortho or para isomer or both. We therefore measured the rate of iodination of phenol, o-iodophenol and p-iodophenol under pseudo firts order conditions (concentration of the phenol higher than $10.[I_2])^3$. The observed second order rate constants are $7.3x10^3$, $11.7x10^3$ and $1.4x10^3 M^{-1}min^{-1}$ for phenol, o-iodophenol and p-iodophenol respectively. Thus the formation of diiodinated products must come mainly from the iodination of o-iodophenol. It can be seen in the table that when this fact is considered, the o/p ratio takes values similar to those obtained under similar reaction conditions.

TABLE: IODINATION OF PHENOL IN WATER SOLUTIONS[a]

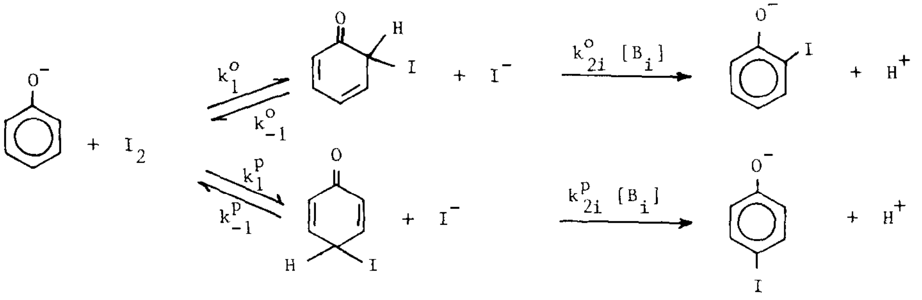
#	[PhOH] (mM)	$[I_2]$ (mM)	$[I^-]$ (mM)	o-I-PhOH[b] %	p-IPhOH[b] %	o/p	pH
1[c,d]	1.62	0.174	4.53	54 ± 2	8.8 ± 0.5	6.1 ± 0.5	7.7
2[c]	5.28	0.579	15.40	57.8 ± 0.8	27.7 ± 0.8	2.1 ± 0.1	7.5
3[c,e]	5.24	0.520	15.20	45.5 ± 0.7	29.8 ± 0.8	1.53 ± 0.06	7.5
4[c,f]	5.24	0.520	15.20	74 ± 3	9.0 ± 0.2	8.2 ± 0.5	6.1
5[c,g]	5.75	0.542	15.30	17.0 ± 0.5	54 ± 2	0.32 ± 0.02	13
6[c]	5.20	0.535	100.0	51 ± 3	16 ± 2	3.2 ± 0.5	7.5
7[h]	2.77	0.525	15.05	55 ± 2	15 ± 2	3.6 ± 0.7	7.5
8[h]	0.360	0.0618	1.842	40.3 ± 0.3	14 ± 1	2.9 ± 0.2[i] (3.1 ± 0.3)[j]	7.5
9[c]	0.550	0.535	15.00	18 ± 1	15.5 ± 0.3	1.2 ± 0.1[k] (2.5 ± 0.1)[j]	7.5
10[l]	0.565	0.590	15.30	15.5 ± 0.3	15.6 ± 0.4	0.99 ± 0.05[m] (2.2 ± 0.1)[j]	7.5
11[n]	0.615	0.575	15.20	22 ± 1	16 ± 2	1.4 ± 0.2[o] (2.7 ± 0.4)[j]	7.5

a) All reactions were carried out at room temperature with magnetic stirring. The pH was maintained with buffer $KPO_4H_2 = 4.25x10^{-3}$ M and $Na_2PO_4H = 2.075x10^{-2}$ M unless otherwise indicated. The concentrations of PhOH, I_2 and I^- indicated are initial concentrations. b) The % is based on the molar amount of the component which has smaller concentration. The phenols where quantified by gas chromatography with 1-bromonaphthalene as internal standard. c) A water solution of PhOH and Buffer is added to a water solution of I_2/I^-. d) $[KPO_4H_2] = 1.27 \times 10^{-3}$ M and $[Na_2PO_4H] = 6.22x10^{-3}$ M. e) $[KPO_4H_2] = 8.65 \times 10^{-3}$ M and $[Na_2PO_4H] = 4.13 \times 10^{-2}$ M. f) $[KPO_4H_2] = 2.17 \times 10^{-2}$ M and $[Na_2PO_4H] = 3.3 \times 10^{-3}$ M. g) $[NaOH] = 1 \times 10^{-1}$M. h) A water solution of I_2/I^- is added dropwise to a water solution of all the other ingredients. i) 3% of diiodophenol is formed. j) Considering that all the diiodophenol comes from the o-iodophenol initialy formed. k) 21% of diiodophenol is formed. l) A water solution of I_2/I^- is added to a water solution of all the other ingredients. m) 19% of diiodophenol is formed. n) 130 ml of a water solution of I_2/I^- is added in portions of 20 ml to 70 ml of a water solutions of all the other ingredients. o) 21% of diiodophenol is formed.

Part of the observed changes in the o/p ratio might be due to the fact that distinct iodinating species predominate under different reaction conditions, and each of them have different selectivity for the ortho and para position[4].

The intervention of IOH and IOH_2^+ as iodinating agents was suggested on the bases of kinetic studies[5]; however, other authors have explained the same results as well as their own considering that I_2 is the only iodinating agent in acidic aqueous solutions of iodine[6]. The ratio I_2/IOH at pH 7 is approximately 10^6 $[I^-]$[7], then the increase in I^- concentration by a factor of 6.5 (runs 2 and 6) implies an increase of the I_2 concentration relative to IOH. And, if these two species had different selectivity for the o- and p- position a change in the o/p ratio would be expected; however, the observed values for the o/p ratio in runs 2 and 6 are the same within experimental error.

On the other hand, there is a significant change in the o/p ratio with the increase in buffer concentration and in the pH under conditions where there is not diiodination. The mechanism of the iodination of phenol under the condition of this study with I_2 as iodinating agent can be represented as in the scheme where B_i stands for any base.



SCHEME

The observed rate constants, assuming a steady state for the cyclohexadienide intermediates, are given by eq. 1 and 2:

$$k^o = \frac{k_1^o \sum k_{2i}^o \; [B_i]}{k_{-1}^o [I^-] + \sum k_{2i}^o [B_i]} \qquad (1) \qquad k^p = \frac{k_1^p \sum k_{2i}^p \; [B_i]}{k_{-1}^p [I^-] + \sum k_{2i}^p [B_i]} \qquad (2)$$

From data reported in the literature[6,8] the ratio $\sum k_{2i} [B_i]/k_{-1}$ in equations 1 and 2 can be estimated as $\sim 10^{-5}$, then these equations are simplified to eq. 3 and 4:

$$k^o = \frac{k_1^o}{k_{-1}^o[I^-]} \sum k_{2i}^o \ [B_i] \qquad (3) \qquad\qquad k^p = \frac{k_1^p}{k_{-1}^p \ [I^-]} \sum k_{2i}^p \ [B_i] \qquad (4)$$

Under the condition of our experiments the Bi are OH$^-$ and/or the basic constituents of the buffer (PO$_4$H$^=$ and PO$_4$H$_2^-$) thus, the ratio o/p can be represented as in eq. 5:

$$\frac{[o]}{[p]} = \frac{1}{2} \ \frac{k_1^o}{k_{-1}^o} \ \frac{k_{-1}^p}{k_1^p} \left[\frac{k_2^o \ [OH] \quad + \sum k_{2Bi}^o \quad [Bi]}{k_2^p \ [OH] \quad + \sum k_{2Bi}^p \quad [Bi]} \right] \qquad (5)$$

Since the increase in buffer concentration as well as the increase in pH bring about a significant decrease in the o/p ratio, k_2^p and k_{2Bi}^p must have a higher value than k_2^o and k_{2Bi}^o respectively[9]. Work is in progress to determine if this behaviour is common to other aromatic substrates.

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3 - Reactions were carried out in the thermostated cell of U.V. spectrophotomether measuring the rate of disappearance of I_3^- at 358 nm. The concentration used where [PhOH] = 5x10^{-4}M, [I$_2$] = 5x10^{-5}M, [I$^-$] = 6x10^{-3}M, [Na$_2$PO$_4$H] / [KPO$_4$H$_2$] = 4.88 total buffer conc. 2.5x10^{-2}M. Reactions were initiated by addition of a concentrated water solution of the corresponding phenol to a solution containing all the other ingredients.

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9 - This conclusion is consistent with the expected steric interference between I and O$^-$ in the ortho product. We thank the Referee for pointing it out.

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